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Therapeutic Approaches to Genital Warts

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Although many treatments are available for genital warts caused by human papillomavirus (HPV), none are uniformly successful in the treatment of this disease. Most current treatment options work by destroying affected tissue, either by a cytotoxic or a physically ablative mode of action. Interferons have antiviral, antiproliferative, and immunomodulatory activities, but these have not translated into a high level of cure rates against warts. With all current treatments, recurrent warts are common. Therapies currently being investigated include a 5-fluorouracil/epinephrine collagen gel that achieves high concentrations of 5-fluorouracil at the site of injection. Other new treatment modalities focus on activating the host's immune system or improving the delivery of therapeutic compounds to the affected site. Imiquimod, a novel immune-response modifier, induces interferon and a number of other endogenous cytokines. A cream formulation containing 5% imiquimod resulted in good total clearance rates and generally tolerable side effects in controlled clinical trials of patients with external genital warts. Perhaps the most effective means for managing HPV disease would be a vaccine that prevents the occurrence of genital warts. Although it is unlikely that such a vaccine will be introduced in the near future, preliminary studies indicate that it may be possible to develop suitable prophylactic and therapeutic vaccines. *Am J Med.* **1997;102(5A):28–37.**

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There are no simple, routinely effective therapies available for the treatment of genital warts, a disease caused by human papillomavirus (HPV). The lack of such therapy often makes the treatment of genital warts a frustrating experience for both the patient and the clinician.

For many diseases, there is little question as to whether offering treatment to a patient is appropriate. Therapy for genital warts is more problematic, however, as some of the recognized goals for treating bacterial sexually transmitted diseases are not necessarily accomplished by treatment of genital warts.[1] Current therapies have a low effectiveness in preventing wart recurrence, and there is little evidence that treatment reduces the likelihood of disease transmission. In many cases, the best that can be hoped for is a temporary reduction of symptoms.

Nevertheless, because genital HPV infections are cosmetically unacceptable and may be associated with discomfort and physical and psychosocial dysfunction, treatment is generally offered to all patients with genital lesions. Other rationales for treatment include the amelioration of symptoms, particularly during wart-free periods, and the possibility of decreased infectivity, not only of HPV, but of other blood-borne infections whose transmission may be enhanced by friable genital warts. Furthermore, in very rare instances, HPV types normally found in genital warts are capable of producing verrucous squamous cell carcinoma (e.g., giant condylomata of Buschke-Löwenstein).

Although experience indicates that most of the current therapies eventually remove warts, recurrences are common. Recurrent warts may be caused by activation of latent virus present in normal skin adjacent to the lesions.[2] New therapies are attempting to improve the efficacy of current treatments by stimulating the host's immune system to eradicate viral infection or by enhancing delivery of therapeutic compounds to HPV-associated lesions.

This article reviews the treatment options available for patients with genital warts, with a focus on new therapies for this disease. These investigational therapies may soon expand the options currently available for the treatment of genital warts.

CURRENT THERAPIES FOR GENITAL WARTS

Many of the therapies used to treat genital warts have been available for decades. In many cases, the

TABLE I
Summary of Selected Published Data on Cytotoxic and Physically Ablative Therapies for Human Papillomavirus Infection

Treatment	Average No. of Treatments (range)*	Success Rates (range)*	Recurrence Rates (range)*	References
Cytotoxic agents				
Trichloroacetic acid (Tri-Chlor)	4.0	64–81%	36%	[3, 4]
Podophyllin (Pod-Ben-25, Podocon-25, Podofin)	3.4–6.7	38–79%	21–65%	[7–14]
Podofilox (Condylox)	3.2 treatment cycles (patient applied)	68–88%	16–34%	[12, 14, 18, 19]
5-FU (Efudex, Fluoroplex)	2–2.5 treatment cycles (patient applied)	68–97%	0–8%	[20, 21]
Physically ablative therapies				
Cryotherapy	2.6–3.2	70–96%	25–39%	[3, 4, 7, 11, 26]
CO_2 laser	1.0–2.0	72–97%	6–49%	[21, 28–31]
Electrodesiccation	1.3	94%	25%	[11]
LEEP	NR	72%	51%	[31]
Surgical excision	1.1	89–93%	19–22%	[10, 13]

5-FU = 5-fluorouracil; LEEP = loop electrosurgical excisional procedure; NR = not reported.
*Ranges are reported where possible; not all papers reported data on all of the parameters included in this table.

safety and effectiveness of these treatments have not been assessed in well-controlled, prospective clinical trials. Comparative trials of therapies are also relatively rare. The dearth of such information can make it difficult to evaluate the efficacy of different treatment modalities.

Table I summarizes selected published data on current genital wart therapies. It should be noted that a number of factors can influence the figures presented in this table. In particular, the location and extent of genital warts, the sex of the patients studied, the treatment regimen, and the quality of care can all be important factors in the success of therapy. Both success and recurrence rates are also heavily affected by the time of assessment; in studies with low recurrence rates, patients may simply have been examined for a shorter time period than in studies with high recurrence rates. All of these factors should be kept in mind when evaluating different studies and therapies.

Cytotoxic Agents

Cytotoxic therapies eliminate genital warts by destroying the affected tissue, either through chemodestructive or antiproliferative modes of action. The therapies described in this section are all applied topically. Unlike surgical procedures, cytotoxic therapies do not generally require local anesthesia. Nevertheless, cytotoxic agents are not painless; local skin reactions are common and in some cases can be severe. The relative merits of various cytotoxic agents are shown in Table I.

Trichloroacetic Acid

Trichloroacetic acid (TCA; trade name, Tri-Chlor) is a chemodestructive agent that causes chemical coagulation of genital warts. An 80–90% solution of TCA is applied directly to the genital wart in the clinic or the physician's office. This treatment can be repeated weekly if necessary. Although TCA has little systemic toxicity, lack of control over the depth of penetration and breadth of the treatment area may result in discomfort and, in rare cases, ulcers and scarring.[3] TCA is effective in the initial destruction of external genital warts and works best when used to treat small, moist warts. As TCA is not absorbed in the general circulation, this compound can be used to treat pregnant patients. However, early recurrences may be frequent. In one study, 36% of treated patients had new lesions within 2 months.[4]

Podophyllin

Podophyllin, a plant compound that causes tissue necrosis by arresting cells in mitosis, is frequently used in the treatment of external genital warts. Podophyllin is applied to warts at concentrations of 10–25% in compound tincture of benzoin. After 1–4 hours, the compound should be thoroughly washed off. Podophyllin is usually applied once weekly for up to 6 weeks.

Current recommendations advise that podophyllin application be limited to <0.5 mL or <10 cm^2 per session to decrease the potential for systemic effects, including bone marrow depression. The systemic toxicity of podophyllin precludes its use during pregnancy.[5] In addition, recent studies have indicated that podophyllin resin may contain mutagenic substances.[6] Podophyllin treatment causes local skin reactions, including redness, tenderness, itching, burning, pain, and swelling.

Approximately 50% of patients respond to treatment, but warts recur in about 40% of them.[7–14] Be-

cause podophyllin is not a standardized compound, the efficacy of different batches may vary significantly.[15,16] In addition, podophyllin is ineffective on relatively dry anogenital areas, including the penile shaft, scrotum, and labia majora.[16]

Podofilox

Podofilox (also known as podophyllotoxin), the major biologically active lignan of podophyllin resin, is available by prescription as a 0.5% solution for self-application to external genital warts. Treatment of genital warts with podofilox solution involves twice-daily application with a cotton swab for 3 days, followed by 4 days without treatment. This cycle can be repeated 4–6 times as necessary. It is recommended that treatment with podofilox be limited to a wart area of ≤ 10 cm^2. Pregnant women should not use podofilox.[5]

Podofilox has several advantages over podophyllin, including a standardized formulation and self-administration by the patient. In addition, podofilox has a lower degree of systemic absorption than podophyllin.[17] Comparative studies indicate that podofilox is more effective and results in faster resolution of warts than podophyllin.[12,14] However, as with podophyllin, recurrent warts are common following podofilox treatment. Recurrences occur in approximately one third of previously resolved warts during the first month after treatment.[18,19]

5-Fluorouracil

The antimetabolite 5-fluorouracil (5-FU) inhibits cell growth by interfering with DNA and RNA synthesis. Topical treatment with 5% 5-FU cream can be helpful in the treatment of some forms of genital warts. In the small studies that have been conducted, about 75% of patients experienced clearance of warts; recurrence rates of <10% have been reported.[20,21]

Although topical treatment with 5-FU does not appear to result in significant systemic toxicity,[20] because it is a teratogen its use is contraindicated during pregnancy. The major drawback of 5-FU therapy is a high level of local irritation. Because of this effect, some patients are unable to tolerate treatment.[22] Vaginal ulcerations and one report of vaginal adenosis with clear cell carcinoma have prompted some clinicians to avoid using 5-FU for the treatment of vaginal condylomata.[23,24] However, this agent may be useful for the treatment of vulvar, perianal, penile, and meatal warts. A thin layer of cream is usually spread over freshly cleaned lesions 1–3 times per week. Depending on the sensitivity of the location, the cream should be washed off after 3–10 hours. Applications may continue for several weeks as needed. Because of the possibility of periconceptual fetal toxicity, the patient should be protected from pregnancy, preferably by oral contraceptives, during 5-FU therapy.[25]

Physically Ablative Therapies

There are a number of physically ablative procedures that have been used to destroy genital warts. Although these techniques often achieve reasonable initial success rates, recurrence rates can also be high (Table I). In addition, physically ablative therapies are painful, and anesthesia is usually required.

Cryotherapy

Cryotherapy, usually with liquid nitrogen as the cryogen, can be used to treat genital and anal warts in patients who do not have extensive disease. Cryotherapy results in the freezing and destruction of the wart and a small area of surrounding tissue.

Cryotherapy clears warts in approximately 75% of patients.[3,4,7,11,26] One comparative study found that cryotherapy was more effective than podophyllin in the treatment of condylomata acuminata, resulting in the elimination of genital warts in 79% of patients treated with cryotherapy, compared with 51% in the podophyllin-treated group. At 6 weeks' follow-up, warts recurred in 21% (30/144) of patients.[7]

In cryotherapy, a cryoprobe, modified Q-tip, or fine spray is used to apply liquid nitrogen to the wart. Freezing is usually continued until a frozen area slightly larger (1–2 mm) than the diameter of the wart is formed. This procedure can be repeated at 1- or 2-week intervals; typically, only two or three sessions are required.

Cryotherapy can be painful, but this effect can usually be managed by the use of a local anesthetic. Because there are no systemic effects, cryotherapy can be used to treat genital warts in pregnant women.[27]

Laser Therapy

Properly performed CO_2 laser treatment has achieved excellent results in the treatment of genital warts.[21,28–31] Recurrence rates vary from low (6–17%)[21,28–30] to high (49%).[31] Laser therapy has been successful in the treatment of penile, anorectal, and urethral warts in men[30] and flat warts of the vagina in women.[31] Laser treatment is also a popular choice for the treatment of lesions that have not responded to other therapies and for extensive HPV disease, because the precision of this technique allows normal adjacent tissue to be spared. As with cryotherapy, there are no systemic effects with laser therapy, so it may be safely performed during pregnancy.[32]

The major drawbacks of laser therapy are the special training and expensive equipment required for treatment. Anti-infective measures must be closely

followed during laser therapy. It is essential that a fume evacuator be used to prevent the inhalation of allergens and HPV DNA found in laser plumes.[33] It is not yet known whether HPV DNA spread by laser energy onto treatment fields and the surrounding normal tissue causes recurrent disease.[34]

Because the procedure is associated with extreme heat, local or general anesthesia is required for laser treatment. In unskilled hands, severe thermal damage to underlying tissue can occur. Side effects include pain, itching, and swelling.

Electrosurgery

Electrosurgical methods use high frequency current to destroy (fulgurate) tissue affected by genital warts. In many cases, local anesthesia is sufficient for patients undergoing this procedure.

Electrodesiccation. Although electrodesiccation is commonly used in the treatment of genital warts, few studies on this technique have been published. In one comparative study, electrodesiccation was found to result in a higher rate of complete wart clearance than podophyllin or cryotherapy (94% vs 41% and 79%, respectively).[11] All three treatment groups were found to have similar recurrence rates in the same range. Another advantage of electrodesiccation was the number of treatments required, a mean of 1.3 compared with >3 for the other two therapies.

Loop electrosurgical excisional procedure. Loop electrosurgical excisional procedure (LEEP) combines electroexcision and fulguration. In many clinics, it has replaced traditional electrosurgical techniques in the treatment of cervical intraepithelial neoplasia (CIN)[35] and external condylomata.[31] In the latter case, the lesion is elevated by a local anesthetic solution or saline (if the patient is treated under general anesthesia), and a small loop electrode is inserted into the superficial dermis (Figure 1).[36] This technique works best with larger, pointed warts; smaller, papular lesions are best treated by electrodesiccation.

A comparative study in >200 male and female patients found that the efficacy and adverse effects of LEEP are similar to those associated with laser ablation in the treatment of external condylomata.[31] Furthermore, LEEP resulted in less blood loss and a shorter operating time than did laser ablation or cold knife conization.[37]

Local anesthesia is typically given to patients with localized lesions, whereas those with extensive disease require general anesthesia. The most common side effect of LEEP for external anogenital condylomata is perioperative bleeding. If the loop electrode penetrates deep into the dermis, bleeding and scarring may result. Because scarring of the penis can result in dysfunction, most physicians prefer CO_2 laser vaporization or cryotherapy over LEEP for penile warts. Infections occur infrequently and can usually be controlled by antibiotics.

Surgical Excision

Surgical tangential excision using either cold knife or scissors has a high success rate in the treatment of genital warts, resulting in approximately 90% wart clearance rates and about 20% recurrence rates.[10,12] Although this technique is often reserved for extensive disease or refractory cases, surgical excision is also successful in the treatment of isolated warts. Compared with other physically ablative methods, surgical excision by a skilled physician is associated with good healing and less pain.

Interferons

Interferon (IFN) is an attractive candidate for the treatment of warts because it has immunomodulatory and antiproliferative effects as well as antiviral activity. Despite its antiviral effects, however, there is evidence that IFN therapy does not eradicate viral infection.[38]

To date, only IFN-α, the form of IFN produced by virus-infected leukocytes or lymphoblasts, is approved for intralesional use in the treatment of genital warts. Accordingly, most studies have been conducted with either natural or recombinant IFN-α. Various routes of IFN administration, including intralesional, topical, and parenteral, have been assessed in patients with genital warts (Table II).

Intralesional Therapy

Intralesional IFN treatment involves injections of the compound into the base of each wart. For recombinant IFN-α 2b (Intron A), injections are performed three times a week for 3 weeks, while for natural IFN-α (Alferon N), injections are performed two times a week for 8 weeks. For Intron, a maximum of five lesions can be treated at one session; the use of Alferon is limited by the total dose.

Controlled clinical trials have indicated that intralesional IFN therapy is more effective than placebo in clearing genital warts. In one study, 62% of pa-

TABLE II
Efficacy of Interferon in the Treatment of Genital Warts

Route of Administration	Clearance Rates (Range)	Recurrence Rates (Range)	References
Intralesional	36–53%	21–25%	[39–41]
Topical	33%	NR	[43]
Systemic	7–82%	23%	[8, 44, 45]

NR = Not reported.

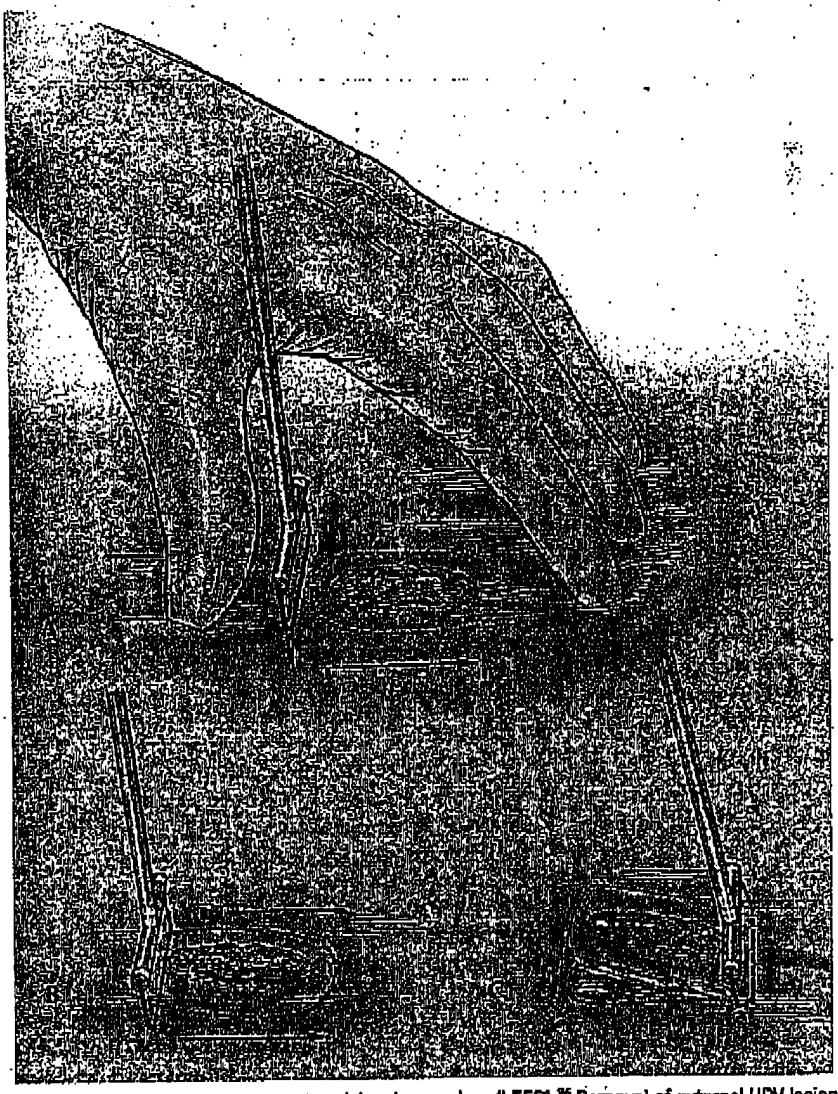

Figure 1. The loop electrosurgical excisional procedure (LEEP).[35] Removal of external HPV lesion with the use of LEEP. (A) The skin around the lesion is stretched with the nondominant hand. (B) The loop is introduced superficially slightly into the dermis. (C) The lesion is removed by drawing the loop of the probe underneath the lesion and out on the other side.

tients treated with natural IFN-α had complete wart clearance, compared with 21% of placebo-treated patients.[30] Similarly, in a trial in which recombinant IFN-α was injected into single warts, a clearance rate of 53% was observed, compared with 14% for placebo-treated patients.[40] Another trial of recombinant IFN showed a lower incidence of complete clearance of IFN-treated warts (36% vs 17% for placebo) but found that the mean wart area decreased almost 40% from initial size in IFN-treated warts compared with an increase of 46% in warts treated with placebo.[41] Recurrence rates of approximately 20–25% have been reported in studies that included a follow-up assessment.[39,41]

Although intralesional IFN therapy helps to limit IFN's systemic effects, flulike symptoms are a common side effect of this treatment. Leukopenia may occur in patients treated for ≥3 weeks. In addition, intralesional administration is a time-consuming and painful procedure.

Topical Administration

Topical creams containing IFN avoid the need for intralesional injections and have minimal side effects.[42] Unfortunately, results obtained with topical IFN have been disappointing. In one clinical trial, the clearance rate in IFN-treated patients approximated 35% and was not significantly different from that re-

ported in the placebo group.[43] Thus, current preparations of topical IFN appear to offer little benefit in the treatment of genital warts.

Systemic Administration

Systemic administration of IFN is another option for selected rare patients with genital warts. In a study in which IFN gamma (IFN-γ) was administered intramuscularly to 28 patients with refractory condylomata acuminata, an overall response rate of 53% was observed.[44] In small studies involving daily subcutaneous or intramuscular injections of IFN-α or IFN-β, clearance rates of approximately 30% have been observed.[42] Recurrence rates have been encouragingly low in some studies,[10] but a larger trial found a recurrence rate of 23% and concluded that podophyllin treatment was significantly more effective than systemic IFN-α.[8]

The adverse effects associated with systemic IFN are substantial. In the small studies conducted to date, all patients experienced systemic adverse reactions.[42] Almost 30% of patients had to discontinue treatment due to adverse effects, and dose reductions were also common.

Adjuvant Therapy With IFN

There are some suggestions that IFN may be a valuable adjunct to conventional therapy, particularly in patients with refractory warts. Although subcutaneous IFN-α did not increase the efficacy of cryotherapy in one controlled trial,[46] another study indicated that prior systemic IFN-γ improved responses to cryotherapy.[44] Similarly, systemic IFN-α has been reported to lower the recurrence rate in patients treated with laser therapy.[47]

Adjuvant therapy with intralesional IFN has also been examined. One combination that has been studied is podophyllin and intralesional IFN.[8] Although adjunctive IFN resulted in a higher rate of complete clearance of warts (67% compared with 42% for podophyllin alone), recurrence rates were similar between the two groups (67% and 65%, respectively). More promising results were obtained when intralesional IFN was used as an adjuvant to either laser or 5-FU therapy. In this instance, a decreased incidence of recurrent anogenital lesions was found in patients who received adjuvant IFN therapy compared with those who did not (7% vs 24%).[48] An independent study of subcutaneous IFN therapy following CO_2 laser therapy found that clearance rates were twice as high in patients receiving adjuvant IFN therapy compared with those receiving placebo.[49]

NEW THERAPIES FOR THE TREATMENT OF EXTERNAL GENITAL WARTS

New therapies for genital warts focus on improving delivery of therapeutic agents to genital lesions and stimulating the immune system to combat the virus. These treatments offer exciting options to conventional treatments and may play an important role in future therapeutic decisions.

5-FU/Epinephrine

An injectable gel containing 5-FU and epinephrine in a protein carrier matrix of purified bovine collagen is being studied for use in the treatment of genital warts and some malignancies. The therapeutic compound in this formulation is 5-FU; epinephrine serves as a vasoconstrictor and acts to retain 5-FU at the site of the lesion.[50] This agent is thus able to maintain high local concentrations of 5-FU at the site of injection.

In a clinical trial of 401 patients with condylomata acuminata, patients received one intralesional treatment of 5-FU/epinephrine gel, 5-FU gel, or placebo per lesion once weekly for up to 6 weeks. A complete response rate of 61% occurred in the group receiving the 5-FU/epinephrine combination, compared with 43% in the group receiving 5-FU alone and 5% in the placebo group. Patients with limited disease (total lesion areas of <100 mm^2) showed the best response to 5-FU/epinephrine, with a complete response rate of 71%; patients with more extensive lesions had a complete response rate of 25%. The 3-month recurrence rate in 5-FU/epinephrine-treated patients whose warts had regressed completely was 39%.[51]

Adverse effects of this therapy include pain during injection and local skin reactions, most notably erythema, swelling, erosions, and ulcerations. No systemic effects were observed in the clinical trial.

Solid-Formulation Podofilox

Gel and cream formulations of 0.5% podofilox have recently been tested for use in the treatment of external anogenital warts. Although the strength of podofilox is the same in the solid formulations as in the solution formulation currently available, the solid formulations are easier to apply and do not require an applicator. The treatment regimen involves application of solid-formulation podofilox twice daily for 3 consecutive days followed by a 4-day rest period. This treatment cycle is repeated until all warts are cleared or for a maximum of 8 weeks.

Although podofilox cream may be more convenient to apply than the solution formulation, its therapeutic efficacy does not appear to be improved. In a comparative study of podofilox cream versus podofilox solution in male patients with genital warts, similar clearance rates and side effects were observed in the two treatment groups.[52]

Podofilox gel has been compared to vehicle gel in a clinical trial, but there are as yet no published data from a comparative trial with podofilox solution. In

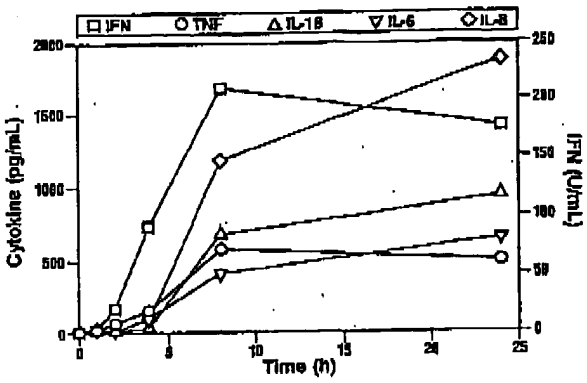

Figure 2. Kinetics of cytokine induction by imiquimod in human peripheral blood mononuclear cells. (Adapted from *J Leukoc Biol*.[57])

316 evaluable patients with anogenital warts, complete wart clearance was observed in 37% of 213 patients after four treatment cycles compared to 2% of 103 patients receiving vehicle gel.[53] After 8 weeks of treatment, 45% of podofilox-treated patients experienced complete wart clearance. Wart recurrence occurred in 32% of successfully treated patients, usually within the first 4 weeks following treatment.

These studies thus suggest that the efficacies of solid and solution formulations of podofilox are similar. However, the improved ease of application may make solid formulations of podofilox an attractive alternative to podofilox solution.

Imiquimod

One immune-response modifier that has recently become the focus of much study is imiquimod. Although imiquimod has no direct antiviral activity, preclinical studies in animal models have demonstrated that imiquimod is a potent inducer of IFN-α and enhances cell-mediated cytolytic activity against viral targets.[54,55] In cell-culture studies with human blood cells, imiquimod resulted in the production of high levels of IFN-α.[56] Imiquimod also induces a variety of other cytokines in human peripheral blood mononuclear cells, including interleukin-1 (IL-1), IL-6, IL-8, tumor necrosis factor (TNF), and IFN. The induction of cytokines is rapid and sustained (**Figure 2**).[57]

Imiquimod 5% cream has been tested in patients with genital warts in five multicenter, double-blind, vehicle-controlled, clinical trials. Patients applied the cream overnight (8 ± 2 hours) three times per week. Treatment was continued for up to 16 weeks or until warts were completely cleared. After a 12-week treatment-free period, the presence of warts was assessed.

Of the 209 patients enrolled in this trial, 109 patients received imiquimod 5% cream and 100 received vehicle cream. Of the 109 patients in the imiquimod 5% group, 36 completed 16 weeks of treatment without totally clearing their warts, 19 withdrew during the treatment period, and 54 totally cleared their warts. Of the 54 patients in the imiquimod 5% group who totally cleared their warts in the treatment period, 39 completed the 12-week follow-up period and remained clear. The other patients were either lost to follow-up or experienced recurrences (**Figure 3**).

Of the 100 patients in the vehicle group, 62 completed the 16 weeks of therapy without totally clearing their warts, 27 withdrew during the treatment period, and 11 totally cleared their warts. Of the 11 patients in the vehicle group who totally cleared their warts in the treatment period, 9 completed the 12-week follow-up period and remained clear. The other patients were either lost to follow-up or experienced recurrences (Figure 3).

The patients treated with imiquimod 5% cream had clearance rates of 50% (72% of females, 33% of males), which were significantly higher than those in patients receiving vehicle cream, who had total clearance rates of 11% (20% of females, 5% of males).[58]

Higher clearance rates were observed in females than in males, possibly due to differences in keratinization of wart tissue.

Local skin reactions, including erythema (61%), erosion (30%), and excoriation/flaking (23%), were the most commonly reported treatment-related events. These reactions were usually mild to moderate in intensity. Overall, 1.2% (4/327) of the patients discontinued due to local skin/application-site reactions.[59]

These data suggest that topical imiquimod may have several advantages over conventional agents in the treatment of external genital warts. Imiquimod is easily applied by the patient and results in acceptable total clearance rates. Systemic side effects are negligible, and local effects are generally tolerable. Topical administration of imiquimod may thus be a suitable therapeutic choice for first-line treatment of external genital warts.

PROSPECTS FOR A VACCINE

As a viral disease, HPV infection is a candidate for preventative vaccination.[64] A successful vaccine could potentially reduce the number of cases of HPV-associated genital cancers, particularly cervical malignancies. Current efforts are targeted at the development of prophylactic vaccines to prevent HPV disease and therapeutic vaccines that help boost the host's immune response to HPV-infected cells.

Because HPV cannot be cultured, most attention to date has been focused on the possibility of a vaccine composed of a specific HPV subunit. Such a

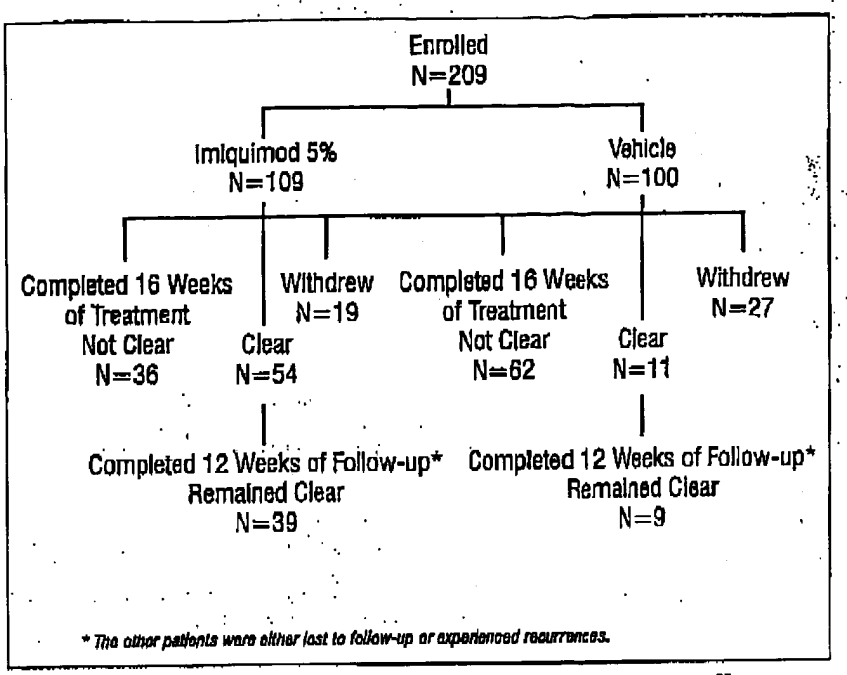

Figure 3. Imiquimod patient accountability for Study 1004 clinical trial.[58]

strategy has been successfully employed in the development of a vaccine for the hepatitis B virus. Potential candidates for an immunogenic HPV subunit include the major and minor capsid proteins L1 and L2. L1, by itself or with L2, can self-assemble into virus-like particles that have a conformation similar to that of intact virions.[60,50] In animal model systems, immunization with these virus-like particles results in the production of antibodies capable of neutralizing the intact virus.[61,62] Alternatively, peptides from the E6 or E7 proteins—the HPV-transforming proteins—are a possible source of a prophylactic or therapeutic vaccine against HPV-associated malignancies.[61]

A potential difficulty with vaccines for genital warts is that >20 different types of HPV can cause genital lesions.[63] Accordingly, effective vaccination will require either the identification of a common antigenic epitope or the development of a multivalent vaccine directed against the relevant HPV types.

CONCLUSIONS

A variety of therapies are available for the treatment of genital warts. The best choice of treatment for a given patient depends on the extent and location of disease and the preferences of the clinician and patient.

Current therapies for the treatment of genital warts probably do not eradicate the viral reservoir present in adjacent tissue. Thus, in many cases these treatments are destined to fail, as indicated by the high rate of recurrent infections. Despite the high recurrence rates associated with current therapies, however, wart clearance is usually achieved in the majority of patients. In some cases, several therapies must be tried over a period of a few months to a year. Even when warts do recur, the patients receive some benefit from a sustained wart-free period.

There is little doubt, however, that new therapeutic options would be a welcome addition to the arsenal of treatment modalities available for genital warts. By prompting the host to join the fight against HPV infection, new immunomodulatory therapies and vaccines hold promise for increasing the success rate of treating genital warts. Improving the delivery of therapeutic compounds to the site of infection may also produce beneficial results.

None of the therapies studied to date purports to be a "cure" for HPV infection. However, with every advance in the treatment of genital warts, more is learned about this disease and the optimal method of combating it. Most importantly, these advances may translate into reduced pain and discomfort for patients with genital warts.

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